coupled hIL13 into animals bearing actively growing glioblastoma tumors caused a significant reduction in the growth rate of the tumors. In some cases, this treatment eliminated any detectable tumors in such animals.

Claims 1-6 were pending in the subject application. By this Amendment, claim 3 has been canceled. Therefore, claims 1-2 and 4-6 are now pending in this application. Consideration of these claims is respectfully requested.

Rejection Under the Doctrine of Obviousness-Type Double Patenting

In the Office Action, claims 1 and 3-5 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14 and 16-20 of U.S. Patent number 5,614,191 (the '191 patent). Specifically, the Office Action indicated that:

> Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The instant claims are generic to the claims of the patent and would have been obvious in view of the patented claims which have all of the characteristics of a method of reducing the rate of growth of tumor cells *in vivo* (claim 20) wherein the tumor cells comprise an IL13-specific receptor comprising delivering into the subject a molecule having an IL13 moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of tumor cells (claims 14 and 16-19). Although the claims are not specifically drawn to the limitations "wherein the rate of the tumor growth is reduced by at least 25%," "wherein tumor volume is reduced," since the method of the patent comprises the same method steps as claimed in the instant invention, that is, administering a molecule comprising an IL13-moiety and a cytotoxin to a mammalian subject with the same population of cells, the claimed method is anticipated and obvious and will inherently lead to at least a 25% reduction in tumor growth and will inherently lead to a reduction in tumor volume.

Applicant respectfully disagrees with this rejection, and points out that, in contrast to the Office Action's assertion, the currently pending claims are not generic (i.e., do not read on) to claims 14 and 16-20 of the '191 patent. For example, nowhere in the claims of the '191 patent is

there a step of delivering into a subject a molecule having an IL13-moiety and a cytotoxic moiety in an effective amount to reduce the growth rate of tumor cells in vivo in a mammalian subject. In fact, claims 14 and 16-19 are silent with regard to where "impairing growth of a solid tumor" occurs. Claim 20 does not necessarily include a step of delivering a molecule into a subject, e.g., the tumor cell could first be contacted with the chimeric molecule in vitro, and then intoduced into a human). Supporting this, the description of the '191 patent does not disclose even one experiment showing administration of a molecule having an IL13-moiety and a cytotoxic moiety to a mammalian subject, much less an experiment showing that delivery of such a molecule inhibits the growth rate of a tumor located within an animal.

An obviousness-type double patenting rejection is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C 103." In re Braithwaite, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Analyzing such a rejection, therefore, parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. In re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); and In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). As such, to make out an obviousness-type double patenting rejection, it must be shown that one of ordinary skill in the art at the time the invention was made would have reasonably expected the claimed invention to work. See In re O'Farrell, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); and In re Dow Chem., 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Given that the invention is within an unpredictable art (i.e., biotechnology), obtaining a particular result in one system (in this case an in vitro assay) does not necessarily mean one will observe a comparable result with a different though analagous system (e.g., within an animal). Thus, without Applicant's present teaching, although it might possibly have been obvious to try to reduce the growth rate of a tumor in an animal

using an IL13-based cytotoxin, there would be no reasonable expectation that this attempt would work, given the substantial differences between in vitro cell cultures and whole animal models. See, e.g., Genentech, Inc. v. Novo Nordisk, 42 USPQ2d 1001 (Fed. Cir. 1997).

In this case, even though the '191 patent discloses that adding an IL13-PE fusion protein to human carcinoma cell lines can inhibit protein synthesis in in vitro assays- this alone does not render obvious the discovery of how to reduce the growth rate of a solid tumor located in situ within an animal. Inhibiting protein synthesis of cultured cell lines in tissue culture is not the same as reducing tumor growth in an animal. In fact, Applicant submits that it is well-known that several substances have been shown to kill cultured tumor cell lines in vitro do not have the same effect when delivered to an animal having a tumor. For example, ethanol, as well as many prospective but unsuccessful anti-cancer drugs, kill cancer cell lines in vitro but not cancerous tumors in animals. Among the many reasons for this is that cancer cell lines cultured in vitro often display a much different phenotype than tumor cells within an animal, and that animals are much more complex biological systems than in vitro tissue cultures. For example, it is well known that the tissue/organ surrounding tumors influence both their phenotype and organization. Given this, the applicant believes that, at most, the description and claimed subject matter of the '191 patent might make it obvious to try using an IL13-cytotoxin fusion protein to reduce tumor growth in an animal. Being "obvious to try" not being the standard under 35 U.S.C 103 (see In re O'Farrell, supra), Applicant respectfully requests withdrawal of this rejection.

Rejection Under 35 USC 112 First Paragraph

In the Office Action, claim 3 was rejected under 35 U.S.C. 112, first paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action indicated that:

> Claim 3 is confusing because it recites the phrase "the rate of tumor growth is reduced by at least 25%." The claim is confusing because it is not clear to what the reduced rate is compared.

Although Applicant does not agree with this statement, to expedite prosecution of this application, claim 3 is herewith being cancelled. Therefore, withdrawal of this rejection is requested.

Rejection Under 35 USC 102 In View of U.S. Patent No. 5,614,191

In the Office Action, claims 1 and 3-5 were rejected under 35 U. S. C. 102(b) as being anticipated by U.S. Patent No. 5,614,191. Specifically, the Office Action stated that:

> The claims are drawn to method of reducing the rate of growth of tumor cells in vivo wherein the tumor cells comprise an IL13-specific receptor comprising delivering into the subject a molecule having an IL13 moiety and a cytotoxic moiety in an amount effect to reduce the rate of growth of tumor cells wherein the rate of the tumor growth is reduced by at least 25%, wherein tumor volume is reduced.
>
> US Patent No, 5,614,191 teaches a method of impairing growth of a solid tumor cell bearing an IL-13 receptor comprising contacting said tumor cell with a molecule comprising an effector molecule attached to IL-13, wherein the effector molecule is a cytotoxin (claims 14 and 16-19), PE38QQR (see Example 4, col. 21- col 22), wherein said tumor cell growth is tumor cell growth in a human (claim 20). Since the method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering a molecule comprising an IL13-moiety and a cytotoxin to a mammalian subject with the same population of cells, the claimed method is anticipated because the method will inherently lead to at least a 25% reduction in tumor growth and will inherently lead to a reduction in tumor volume. See Ex Parte Novitski 26 USPQ 1389 (BPAI 1993).

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention `not novel' or `anticipated' within section 102, the stated test is whether a reference contains an `enabling disclosure' . . . ." In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). In contrast to the Office Action's assertion, Applicant submits that the '191 patent does not disclose, in an enabling manner, a "method of reducing the growth of tumor cells in vivo in a mammalian subject, the tumor cells comprising an IL13-specific receptor, comprising the step of delivering into the subject a molecule having an IL13-moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of tumor cells."

First, albeit the '191 patent states that a chimeric molecule can be administered to a human to impair tumor growth in a human, no specific data is shown that supports that this method would work in a human. Moreover, the '191 patent does not indicate that a step of delivering a chimeric molecule to a human (or even a laboratory animal) was ever attempted. Rather, the only data to supporting the use of such chimeric molecules to inhibit cancer cell growth are from in vitro experiments. See Example 4 of the '191 patent. In these in vitro studies, adding a chimeric molecule to various carcinoma cell lines in tissue culture reduced the level of protein synthesis in these cells. No data, however, was presented to show that the carcinoma cell lines tested in Example 4 expressed an IL13-specific receptor (i.e., one that does not bind hIL4; see p. 16, lns. 20-22 of the present specification). In fact, the data presented suggested just the opposite conclusion - that the receptor targeted by the chimeric molecule in

this case is one that binds both IL4 and IL13 (because adding hIL4 to the tissue cultures reduced the ability of the chimeric molecule to inhibit protein synthesis). In addition, the '191 patent did not present data from actual experiments to show what "an amount effective to reduce the rate of growth of tumor cells" was.

For the foregoing reasons, Applicant submits that none of the currently pending claims are anticipated by the '191 patent, and therefore respectfully requests withdrawal of this rejection.

Rejection Under 35 USC 102 In View of Debinski et al. and Lopes et al.

In the Office Action, claims 1-5 were rejected under 35 U. S. C. 102(a) as being anticipated by Debinski et al. as evidenced by Lopes et al. Specifically, the Office Action stated that:

> The claims are drawn to a method of reducing the rate of growth of tumor cells in vivo wherein the tumor cells comprise an IL13-specific receptor, wherein the tumor cells are glioblastoma multiforme cells, comprising delivering into the subject a molecule having an IL13 moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of tumor cells wherein the rate of the tumor growth is reduced by at least 25%, wherein the tumor volume is reduced. Lopes et al teach that U-251 MG is a human glioblastoma multiforme cell line (see abstract). Debinski et al teach administration of hIL13 based cytotoxins which cured 25 to 40% of SCID mice bearing intracranial U-251 MG glioma xenografts. The reference further teaches that the majority of human glioblastoma cell lines over-express large numbers of receptor for IL13 and that the results in SCID mice provide unequivocal support for the restrictive hIL13R being the marker of GBM and finally teach that the marker can serve for the delivery of anti-GBM therapies. It is clear that since the tumors were cured, growth of the tumor was reduced by at least 25%. Since the method of the prior art comprises the same method steps as claimed in the instant invention, that is, administering a molecule comprising an IL13-moiety and a cytotoxin to a mammalian subject with the same population of cells, the claimed method is anticipated because the method will inherently lead to a reduction in tumor volume. See Ex Parte Novitski 26 USPQ 1389 (BPAI 1993).

The Debinski et al. reference is an abstract that discloses only the conclusion that hIL13-based cytotoxins cured 25-40% of SCID mice bearing intracranial U-251 glioma xenografts.

How such cures were actually achieved is not disclosed. For example, Debinski et al. does not mention the dosage, regimen, method of delivery, method of implanting the tumor and its localization, etc. The Debinski et al. reference does not even mention the form of IL13-based cytotoxin used in the study. Thus, using the Debinski et al. reference as a guide, even one skilled in the art would have to apply undue experimentation to determine how to make the claimed invention. The reference cannot, therefore, anticipate the presently claimed invention. Accordingly, withdrawal of this rejection is requested.

Rejection Under 35 USC 103 In View of U.S. Patent No. 5,614,191 or Debinski et al.

In the Office Action, claims 1 and 6 were rejected under 35 U.S.C. 103 as being unpatentable over U.S. Patent No. 5,614,191 or Debinski et al. More specifically, the Office Action asserted that:

> The claims are drawn to a method of reducing the rate of growth of tumor cells in vivo wherein the tumor cells comprise an IL 13-specific receptor comprising delivering into the subject a molecule having an IL13 moiety and a cytotoxic moiety wherein the delivering is by intratumoral injection.
>
> US Patent No. 5,614,191 and Debinski et al teach as set forth above but do not teach a method wherein the molecule is delivered by intratumoral injection. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer the molecule intratumorally because intratumoral injection of therapeutics was conventional in the art at the time the invention was made. One of ordinary skill in the art would have been motivated to intratumorally inject the molecule in order to avoid the problems associated with, for example, intravenous administration, which results in not only the dilution of the therapeutic but also renders it highly vulnerable to attack by the immune system.

Claims 1-5 were also rejected under 35 U.S.C. 103 as being unpatentable over U.S. Patent No. 5,614,191 in view of Debinski et al. The Office Action asserted that:

The claims are drawn to a method of reducing the rate of growth of tumor cells in vivo wherein the tumor cells comprise an IL13-specific receptor, wherein the tumor cells are glioblastoma multiforme cells, comprising delivering into the subject a molecule having an IL 13 moiety and a cytotoxic moiety in an amount effective to reduce the rate of growth of tumor cells wherein the rate of the tumor growth is reduced by at least 25%, wherein the tumor volume is reduced.

US Patent No. 5,614,191 teach as set forth above but do not teach a method of treatment wherein the tumor cells to be treated are glioblastoma multiforme cells. Debinski et al teach that human glioblastoma multiforme explant cells are extremely sensitive to a chimeric protein composed of hIL 13 and a cytotoxin, PE38QQR (see Abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of US Patent No. 5,615,191 to treat a human patient with human glioblastoma multiforme tumor cells because Debinski et al teach that primary human glioblastoma multiforme cells are extremely sensitive to a chimeric protein composed of hIL 13 and PE38QQR which appears to be the same construct used in the method of US Patent No. 5,615,191. One of ordinary skill in the art would have been motivated to use the method of US Patent No. 5,615,191 to treat a human patient with human glioblastoma multiforme tumor cells because US Patent No. 5,615,191 specifically claims a method of impairing growth of a solid tumor cell bearing an IL-13 receptor and because Debinski et al have clearly taught that human glioblastoma multiforme cells are sensitive to and bind an IL 13 construct and therefore would be expected to express hIL13 receptor.

To establish a prima facie case of obviousness, (1) the prior art reference (or references when combined) must teach or suggest all the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and (3) there must be a reasonable expectation of success. See MPEP 2142. In addition, both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Office Action does not indicate that claimed techniques would have had a reasonable expectation of success in view of the '191 patent. Moreover, for the reasons set forth above

(responding to the 102 rejections), Applicant submits that at the time the invention was made, the cited references, even in combination, did not teach how to practice the claimed method, and did not provide a reasonable expectation that the claimed invention would work. And although the Debinski et al reference disclosed the conclusion that hIL13 based toxins cured mice of glioma xenografts, it did not disclose how this was achieved. It is only with Applicant's present teaching, and not from in vitro data alone or in combination with conclusions but not methodology of in vivo experiments, that one would taught how the claimed method could be performed to effect a reduction in tumor growth rate in an animal. Withdrawal of this rejection is therefore respectfully requested.

Conclusion

Claims 1,2, and 4-6 are now pending in the application; claim 3 having been canceled and by this Amendment. Applicant submits that currently pending claims are supported throughout the specification and are patentable over the prior art. No new matter has been added.

Applicant submits that this application is now in full condition for allowance, which action is respectfully requested.

A Petition for Retroactive Extension of Time and the required fee for a one month extension of time accompanies this Amendment. The Commissioner is hereby authorized to charge any underpayment or credit any overpayment of fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 17-0055.

Applicants invite the Examiner to call the undersigned if clarification is needed on any matter within this Amendment, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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